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published in

Archives of General Psychiatry
2008

DOI (link to publisher)

[10.1001/archpsyc.65.8.897](https://doi.org/10.1001/archpsyc.65.8.897)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

de Moor, M. H. M., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & de Geus, E. J. C. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives of General Psychiatry*, 65(8), 897-905. <https://doi.org/10.1001/archpsyc.65.8.897>

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Testing Causality in the Association Between Regular Exercise and Symptoms of Anxiety and Depression

Marleen H. M. De Moor, MSc; Dorret I. Boomsma, PhD; Janine H. Stubbe; Gonneke Willemsen, PhD; Eco J. C. de Geus, PhD

Context: In the population at large, regular exercise is associated with reduced anxious and depressive symptoms. Results of experimental studies in clinical populations suggest a causal effect of exercise on anxiety and depression, but it is unclear whether such a causal effect also drives the population association. We cannot exclude the major contribution of a third underlying factor influencing exercise behavior and symptoms of anxiety and depression.

Objective: To test causal effects of exercise on anxious and depressive symptoms in a population-based sample.

Design: Population-based longitudinal study (1991-2002) in a genetically informative sample of twin families.

Setting: Causal effects of exercise were tested by bivariate genetic modeling of the association between exercise and symptoms of anxiety and depression, correlation of in-pair differences in these traits among genetically identical twins, and longitudinal modeling of changes in exercise behavior and anxious and depressive symptoms.

Participants: A total of 5952 twins from the Netherlands Twin Register, 1357 additional siblings, and 1249 parents. All participants were aged 18 to 50 years.

Main Outcome Measurements: Survey data about leisure-time exercise (metabolic equivalent task hours per week based on type, frequency, and duration of exercise) and 4 scales of anxious and depressive symptoms (depression, anxiety, somatic anxiety, and neuroticism, plus a composite score).

Results: Cross-sectional and longitudinal associations were small and were best explained by common genetic factors with opposite effects on exercise behavior and symptoms of anxiety and depression. In genetically identical twin pairs, the twin who exercised more did not display fewer anxious and depressive symptoms than the co-twin who exercised less. Longitudinal analyses showed that increases in exercise participation did not predict decreases in anxious and depressive symptoms.

Conclusion: Regular exercise is associated with reduced anxious and depressive symptoms in the population at large, but the association is not because of causal effects of exercise.

Arch Gen Psychiatry. 2008;65(8):897-905

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EPIDEMIOLOGICAL STUDIES¹⁻¹⁰ consistently report a small to moderate cross-sectional association between lack of exercise and depressive symptoms in population-based samples. The association holds using various measures of exercise behavior, and using either the Beck Depression Inventory,^{1,2,8} or the Center for Epidemiological Studies Depression Scale^{4,7,9,10} as a measure of depressive symptoms. Lack of regular exercise is also associated with high levels of anxiety and neuroticism measured using various instruments.^{7,8,11} Longitudinal studies further show that exercise at baseline predicts fewer depressive symptoms at follow-up. Of 9 studies,^{1,3-5,9,10,12-14} 6 studies^{3,5,9,10,13,14} found a prospective associa-

tion. One study⁴ observed an effect only in white women, and another study¹⁵ that examined the association between clinical diagnoses of depressive disorders and exercise behavior in the population found evidence for a cross-sectional association but not for a prospective association.

Experimental studies investigating the effect of exercise training on symptoms of clinical depression and anxiety are numerous, and many reviews¹⁶⁻²² and meta-analyses²³⁻²⁶ have been published. These reviews and meta-analyses often differ in their inclusion criteria with regard to measurement of depression or anxiety (self-reported symptoms or clinical diagnosis), sample characteristics (healthy participants or clinical population), and research design (differences in control

groups, randomization, and periods of training and follow-up). Nevertheless, most authors of these reviews conclude that exercise training seems to relieve symptoms of anxiety and depression. Furthermore, some randomized controlled trials suggest that exercise training reduces depressive symptoms, with effect sizes comparable to those of antidepressant use.²⁷

The evidence from these prospective and experimental studies makes it tempting to interpret the association at the population level as reflecting a causal effect of exercise on the symptoms of anxiety and depression. This explanation fits folk wisdom. However, results from experimental studies may not always generalize to the population at large. There may be ascertainment in these studies such that only subjects attracted to exercise may enroll and persist. Treatment effects in psychiatric patients may not generalize to the extent that exercise relieves mild forms of symptoms of anxiety and depression in healthy participants. Finally, although findings of prospective studies are compelling, they are based on correlations between traits that are time lagged. We cannot rule out that some underlying factors that influence exercise behavior at one time point also influence symptoms of anxiety and depression at a later time point. Genetic variation among individuals is such a potential underlying factor. Exercise behavior and symptoms of anxiety and depression are heritable traits, with genetic factors explaining about 40% to 50% of the variation in anxious and depressive symptoms²⁸ and about 50% to 60% of the variation in exercise behavior.^{29,30} Some genetic factors influencing exercise behavior may overlap with genetic factors influencing anxious and depressive symptoms.

The objective of the present study was to test the causal effects of exercise on reducing anxious and depressive symptoms, taking this potential genetic confounding into account. To this end, we used longitudinal data from genetically informative individuals (twins and their family members) that allows a strong nonexperimental design to test the causal hypothesis in a population-based sample. Specifically, we tested 4 predictions generated by the causal hypothesis.

A first prediction is that, if exercise causally influences symptoms of anxiety and depression, all genetic and environmental factors that influence exercise behavior will also, through the causal chain, influence these symptoms. We can test this in a bivariate model using identical (ie, monozygotic [MZ]) and fraternal (ie, dizygotic [DZ]) twins by computing the genetic and environmental correlations between 2 traits.³¹ Under the causal hypothesis, genetic and environmental correlations should be significant (**Figure 1A**), whereas a significant genetic correlation in the absence of significant environmental correlation falsifies the hypothesized causal effect of exercise.

A second prediction made by the causal hypothesis is that in genetically identical (MZ) twins the within-twin pair differences in levels of exercise participation should be associated with within-twin pair differences in anxious and depressive symptoms. This means that the twin who participates in more exercise should display fewer anxious and depressive symptoms than the co-twin who exercises less (**Figure 1B**). The absence of this relationship between the within-pair differences in

exercise participation and symptoms of anxiety and depression falsifies the hypothesized causal effect of exercise, whereas the presence of this relationship would argue in favor of the causal hypothesis because it excludes confounding by genetic factors (the twins are genetically identical).

A third prediction made by the causal hypothesis is that, if exercise reduces symptoms of anxiety and depression, exercise at baseline should predict anxious and depressive symptoms longitudinally, and this should be independent of genetic factors influencing exercise behavior and symptoms of anxiety and depression. This prediction can be tested in a twin sample by computing the genetic and environmental correlations between exercise and symptoms of anxiety and depression at successive time points (**Figure 1C**). Under the causal hypothesis, longitudinal genetic and environmental correlations should be significant, whereas a significant longitudinal genetic correlation in the absence of significant environmental correlation falsifies the hypothesized causal effect of exercise.

A fourth prediction by the causal hypothesis is that within-subject changes in exercise behavior should predict parallel changes in anxious and depressive symptoms such that increases in frequency and intensity of exercise behavior over time would reduce symptoms of anxiety and depression and that, vice versa, decreases in frequency and intensity of exercise behavior over time would increase symptoms of anxiety and depression (**Figure 1D**). Such a pattern would argue in favor of the causal hypothesis because it excludes confounding by a genetic factor (the subjects' genotypes do not change over time). In contrast, the absence of a correlation between changes in exercise and symptoms over time would falsify the hypothesized causal effect of exercise.

METHODS

PARTICIPANTS

This study was part of an ongoing study on health, lifestyle, and personality in adult twins and their relatives who are voluntarily registered at the Netherlands Twin Register.^{32,33} Since 1991, every 2 to 3 years the participants receive a mailed questionnaire with questions about their health, lifestyle, and personality. Data about exercise behavior (type, frequency, and duration) and symptoms of anxiety and depression were available for 1991, 1993, 1995, and 2002 (**Figure 2**). We included individuals within the age range of 18 to 50 years (ie, at no time point was the age of the participants younger than 18 years or older than 50 years). The mean (SD) age was 27.9 (8.0) years. We excluded 37 twins with unknown zygosity and 47 genetically unrelated siblings and half siblings. In 1991 and 1993, twins and their parents were invited to participate, and data about exercise participation and 3 measures of anxious and depressive symptoms (anxiety, somatic anxiety, and neuroticism, described herein) were collected. In 1991, twins also completed the Young Adult Self Report (YASR)³⁴ depressive symptoms scale. In 1995, twins, siblings, and parents were invited, but only twins answered questions about depressive symptoms (YASR scale). In 2002, twins, siblings, parents, and spouses provided data about exercise participation, and 4 measures of anxious and depressive symptoms were collected. For the longitudinal analyses, only data from twins and parents were used. There were 15 961 twins and parents from 4496 families who participated at least

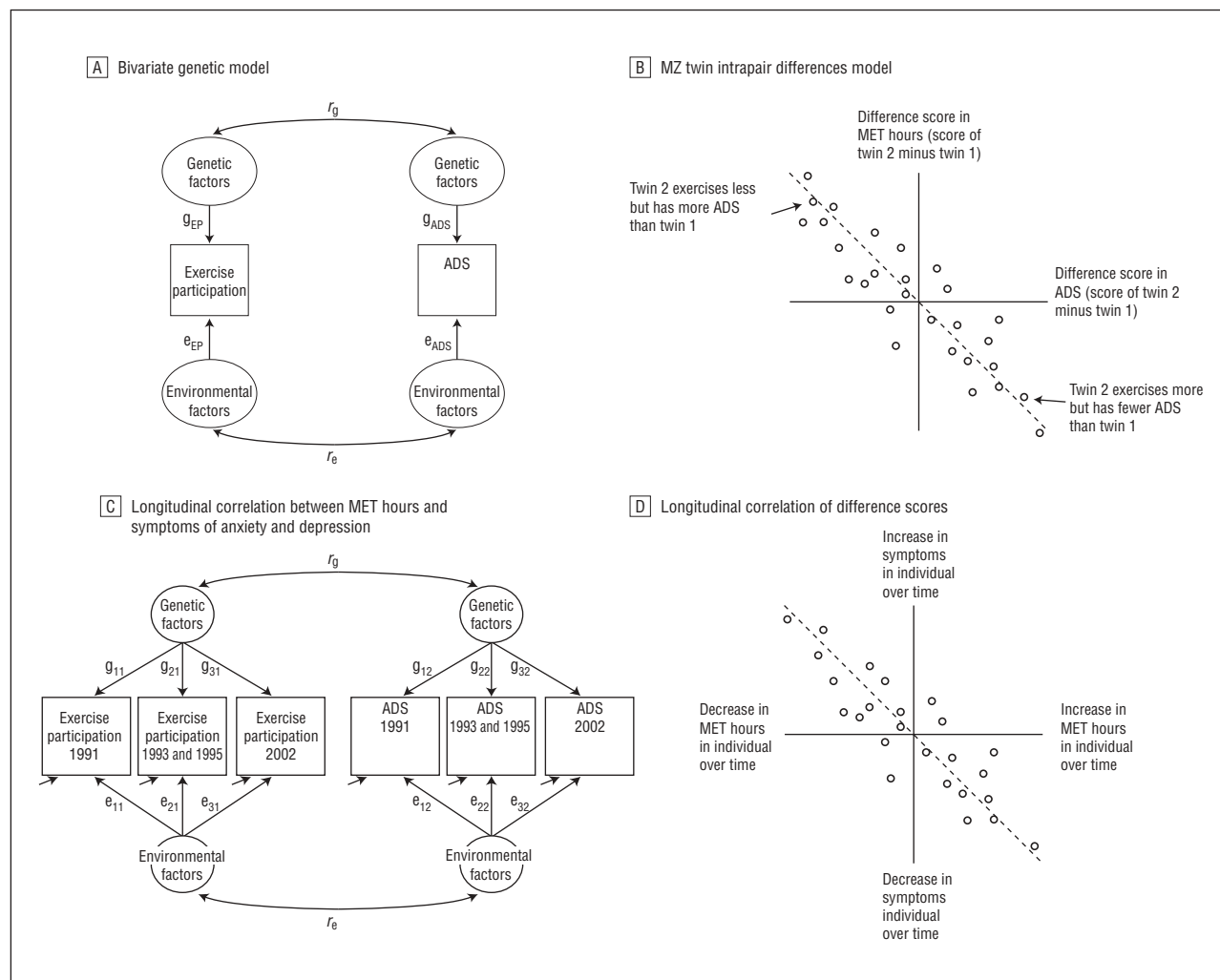


Figure 1. Graphic representation of 4 models used to test the hypothesis that exercise causes reduced symptoms of anxiety and depression. A, A causal effect of exercise predicts significant overlap (ie, correlation) between genetic and environmental factors influencing exercise behavior and anxious depressive symptoms (ADS). Cross-sectional correlation between exercise and ADS = $(g_{EP} \times r_g \times g_{ADS}) + (e_{EP} \times r_e \times e_{ADS})$. B, A causal effect of exercise predicts that in genetically identical twins, the twin who exercises more has fewer ADS. MET indicates metabolic equivalent task. C, A causal effect of exercise predicts significant overlap (ie, correlation) between genetic and environmental factors influencing exercise behavior at an early time point and ADS at a later time point. For example, longitudinal correlation between exercise in 1991 and ADS in 2002 = $(g_{11} \times r_g \times g_{32}) + (e_{11} \times r_e \times e_{32})$. D, A causal effect of exercise predicts that an increase in exercise leads to a decrease in ADS in an individual over time. e indicates environmental factor loading; EP, exercise participation; g , genetic factor loading; MET, metabolic equivalent task; MZ, monozygotic; r_e , environmental correlation; and r_g , genetic correlation.

once in 1991, 1993, 1995, or 2002. Of these, 8662 individuals from 2288 families participated at 2 or more time points. Individuals who participated in more than 1 survey were, on average, less anxious and depressed and more physically active than individuals who participated only once, but the differences are small (data not shown). Similar findings were reported in a study³⁵ in which it was shown that individuals from highly cooperative families are slightly less anxious and depressed but are not more frequent exercisers compared with individuals from less cooperative families.

Zygosity was determined by DNA typing for 33.2% of the same-sex twin pairs. For the other same-sex twins, zygosity was based on 8 items regarding physical similarity and the frequency of confusion between the twins by parents, other family members, and strangers. Agreement between zygosity based on these 8 items and zygosity based on DNA typing was 97%.³⁶

For the cross-sectional analyses, the most recent data from complete twin pairs and a maximum of 1 additional brother and 1 sister were selected. For all measures, data from 2002

were selected first. For all measures except the YASR scale, we next selected data from 1993 and then from 1991. For the YASR scale, we next selected data from 1995 and then from 1991. After this selection of complete pairs, the most recent data of incomplete twin pairs and possible additional siblings were selected. This ensured a maximum of complete twin pairs in the dataset and resulted in a cross-sectional dataset of 941 MZ male, 656 DZ male, 1802 MZ female, 1067 DZ female, and 1486 DZ opposite-sex twins, 586 brothers, and 771 sisters (from 3619 families). Of these, there were 2547 complete twin pairs (406 MZ male, 281 DZ male, 789 MZ female, 455 DZ female, and 616 DZ opposite-sex pairs).

For the longitudinal analyses, there were 1878 twins and parents with valid data about exercise behavior and symptoms of anxiety and depression in both 1991 and 1993, 584 twins and parents with valid data in both 1991 and 2002, and 1037 twins and parents with data in both 1993 and 2002. There were 534 twins with data in both 1991 and 1995 and 1166 twins with data in both 1995 and 2002.

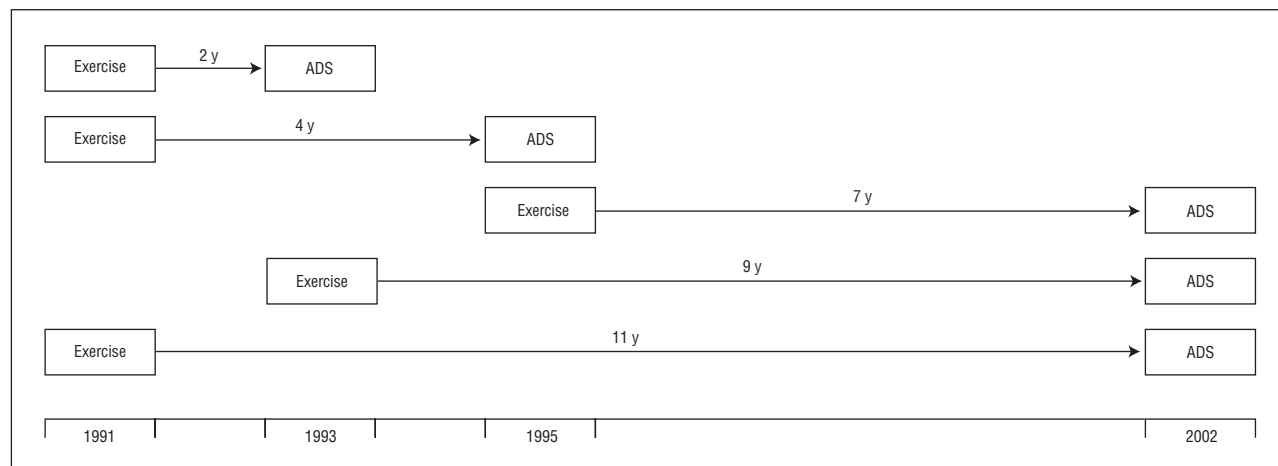


Figure 2. Overview of the longitudinal data regarding exercise behavior and symptoms of anxiety and depression in the Netherlands Twin Registry. ADS indicates anxious depressive symptoms.

MEASUREMENTS

Leisure-time exercise was measured by several questions. The first question asked whether the respondent participated in exercise regularly and could be answered yes or no. If the participant responded in the affirmative, further information about type, frequency, and duration of exercise was gathered. Reported non-leisure-time activities such as walking or biking to work were not counted as exercise. All remaining exercise activities were assigned a metabolic equivalent task (MET) value, using the Compendium of Physical Activities by Ainsworth et al.³⁷ A MET score of 1 corresponds to the rate of energy expenditure when at rest (1 kcal/kg/h). MET hours were computed as MET multiplied by hours per week. Scores of nonexercising individuals were coded as zero. The distribution of MET hours was skewed (distribution, 2.67) and demonstrated kurtosis (distribution, 12.18). Therefore, for the computation of correlations in the bivariate genetic models, log transformation was applied to the MET hours, which significantly reduced the skewness and kurtosis to 0.47 and -1.06, respectively. For computation of the difference scores, we used the untransformed MET hour scores because the difference scores were normally distributed. The test-retest reliability of MET hours was 0.82 as computed among 200 individuals who completed the questions about exercise in December 2004 and again 6 months later.

Anxious and depressive symptoms were measured using 4 continuous scales. Middeldorp et al³⁸ demonstrated that these measures are good predictors for the DSM-IV-based disorders of major depressive disorder, dysthymia, generalized anxiety disorder, panic disorders, and social phobia. Depressive symptoms were measured using the YASR scale (16 items in 3 categories). Anxious symptoms were measured using the State-Trait Anxiety Inventory (20 items on a 4-point Likert-type scale) by Spielberger et al.³⁹ Neuroticism and somatic anxiety were measured using the Amsterdamse Biografische Vragenlijst,⁴⁰ a Dutch questionnaire that is similar in content to the Personality Inventory by Eysenck and Eysenck.⁴¹ The neuroticism scale consists of 30 items and the somatic anxiety scale 17 items (3 answering categories). The somatic anxiety scale contains items about somatic complaints that are related to anxiety and depression such as headaches and sleep problems. Summed scores of each of these measures were computed. For correlations and bivariate genetic modeling, the depression, anxiety, somatic anxiety, and neuroticism scales were transformed before analysis to improve normality according to the recommendations by Boomsma et al²⁸ using the following formulas: 5 times the natu-

ral logarithm (neuroticism), 12 times the natural logarithm (depression), 10 times the natural logarithm (anxiety), and 9 times the natural logarithm (somatic anxiety). The difference scores of the untransformed data regarding anxious and depressive symptoms were normally distributed. We further included a common factor score variable of all measures of anxious and depressive symptoms in the analyses. This common factor score variable was derived in a previous study²⁸ showing that the genetic the genetic variation in these measures derives from common genetic factors.

STATISTICAL ANALYSIS

The first 2 tests of the causal hypothesis (the bivariate genetic model and the MZ twin intrapair differences model) were based on cross-sectional data only. The bivariate genetic model tested whether an association between exercise and symptoms could be explained by an overlap in latent genetic or environmental factors that influence these traits. Similar to decomposition of trait variance in a univariate genetic model in which MZ and DZ cross-twin or sibling correlations are compared,³¹ MZ and DZ cross-twin or sibling cross-trait correlations are compared to evaluate whether covariance between 2 traits can be explained by overlapping additive genetic factors or by overlapping unique environmental factors. If the MZ cross-twin cross-trait correlation is approximately twice the DZ cross-twin or sibling cross-twin or sibling cross-trait correlation, overlapping additive genetic factors are indicated. If the MZ cross-twin cross-trait correlation is smaller than the within-person cross-trait correlation, overlapping environmental factors that are unique to the individual are indicated.

Maximum likelihood estimation (Mplus; Muthén & Muthén, Los Angeles, California)⁴² was used to obtain genetic and environmental correlations.³¹ The hypothesis of a causal effect was tested by constraining the genetic or environmental correlation to zero. If this constraint is allowed (ie, the genetic or environmental correlation between exercise and symptoms of anxiety and depression is zero), a causal effect cannot be the source of their association. This genetic model also allowed us to test whether only the genetic correlation was significant. This would be compatible with the hypothesis of a common genetic factor underlying the cross-sectional association.

Using the MZ twin intrapair differences model, we computed the differences of all measures of anxious and depressive symptoms of an MZ twin and his or her co-twin. These intrapair differences in symptoms were then regressed on the

Table 1. Within-Person Cross-Trait and Cross-Sibling Cross-Trait Correlation Between Metabolic Equivalent Task (MET) Hours and Symptoms of Anxiety and Depression

Variable	Correlation Between MET Hours and									
	Depression		Anxiety		Somatic Anxiety		Neuroticism		Composite Score	
	No. of Pairs	Pearson <i>r</i> (95% CI) ^a	No. of Pairs	Pearson <i>r</i> (95% CI)	No. of Pairs	Pearson <i>r</i> (95% CI)	No. of Pairs	Pearson <i>r</i> (95% CI)	No. of Pairs	Pearson <i>r</i> (95% CI)
Within-Person Cross-Trait Correlations										
Total	6187	-0.09 (-0.12 to -0.07)	6391	-0.10 (-0.12 to -0.07) ^a	6320	-0.11 (-0.14 to -0.09) ^a	6307	-0.09 (-0.12 to -0.07) ^a	6226	-0.12 (-0.14 to -0.09) ^a
Men	2377	-0.09 (-0.13 to -0.05)	2414	-0.06 (-0.11 to -0.02) ^a	2393	-0.07 (-0.11 to -0.03) ^a	2388	-0.06 (-0.10 to -0.02) ^a	2346	-0.08 (-0.12 to -0.04) ^a
Women	3810	-0.10 (-0.13 to -0.06)	3977	-0.12 (-0.15 to -0.09) ^a	3927	-0.14 (-0.17 to -0.11) ^a	3919	-0.11 (-0.14 to -0.08) ^a	3880	-0.14 (-0.17 to -0.10) ^a
Cross-Sibling Cross-Trait Correlations										
Men										
MZ	479	-0.10 (-0.16 to -0.04)	511	-0.07 (-0.13 to -0.01) ^a	510	-0.07 (-0.13 to -0.01) ^a	510	-0.06 (-0.12 to -0.00) ^a	508	-0.09 (-0.14 to -0.03) ^a
DZ	2525	-0.08 (-0.14 to -0.01)	2532	-0.03 (-0.10 to 0.04)	2518	-0.03 (-0.10 to 0.04)	2513	-0.02 (-0.08 to 0.05)	2478	-0.04 (-0.11 to 0.03)
Women										
MZ	943	-0.11 (-0.15 to -0.07)	983	-0.08 (-0.13 to -0.04) ^a	982	-0.12 (-0.16 to -0.08) ^a	982	-0.09 (-0.13 to -0.05) ^a	981	-0.11 (-0.15 to -0.07) ^a
DZ	4149	-0.05 (-0.11 to -0.01)	4237	-0.04 (-0.09 to 0.01)	4315	-0.08 (-0.13 to -0.03) ^a	4208	-0.07 (-0.11 to -0.02) ^a	4172	-0.07 (-0.11 to -0.02) ^a
DZ	4940	-0.06 (-0.11 to -0.02)	5104	-0.04 (-0.09 to -0.00)	5076	-0.03 (-0.08 to 0.02)	5068	-0.05 (-0.09 to 0.00)	5021	-0.05 (-0.10 to -0.00)
Opposite sex										

Abbreviations: CI, confidence interval; DZ, dizygotic; MZ, monozygotic.

^aSignificant based on 95% CIs.

difference in MET hours. Significant (and negative) regression coefficients would be compatible with the causal hypothesis, whereas nonsignificant regression analysis would falsify this hypothesis.

The third and fourth tests of the causal hypothesis were based on the longitudinal dataset. We computed the longitudinal correlation between MET hours and symptoms of anxiety and depression for 2-, 4-, 7-, 9-, and 11-year intervals. Because individuals in the longitudinal dataset were not independent observations but were clustered in families, we used the COMPLEX option in combination with the robust maximum likelihood estimator in Mplus,⁴³ which successfully corrects for bias in standard errors and χ^2 test statistics due to this dependency.⁴⁴ If exercise causes decreased anxious and depressive symptoms in the population, there should be a significant longitudinal association between MET hours at baseline and subsequent symptoms of anxiety and depression. If longitudinal correlations are nonsignificant, the hypothesis of a causal effect is falsified. However, the reverse is not true. A significant longitudinal correlation does not necessarily provide evidence for causality if common genetic factors drive the correlation between MET hours at baseline and symptoms of anxiety and depression at follow-up. We again used the genetic information in our sample to more robustly test causality using the multivariate model shown in Figure 1C. Because of the complexity of the model, this model was fitted to the data in Mx (Department of Psychiatry, Virginia Commonwealth University, Richmond).⁴⁵ As with the cross-sectional data, we tested for a causal effect by constraining the genetic or environmental correlation between exercise behavior and symptoms of anxiety and depression to zero. In this case, the genetic and environmental factors were not based on a single cross-sectional measurement but rather on all available successive measurements of exercise behavior and symptoms of anxiety and depression. If the genetic or environmental correlation between exercise behavior and symptoms can be constrained to zero, a causal effect of exercise cannot be the source of the longitudinal or cross-sectional association. As in the cross-sectional analysis, this genetic model also allowed us to test whether only the genetic correlation was significant. This would be compatible with the hypothesis of a common genetic factor underlying the longitudinal association.

The fourth test of causality was based on the longitudinal correlation of difference scores. If commencement of an exercise regimen causes reductions in anxious and depressive symptoms among the population, an increase in weekly MET hours should predict a decrease in anxious and depressive symptoms over time. Likewise, cessation of regular exercise should be associated with an increase in anxious and depressive symptoms. Regression analyses were performed in Mplus that predicted within-subject changes in symptoms by changes in MET hours. The COMPLEX option and robust maximum likelihood estimator estimator were used to correct for bias due to family clustering of data. To account for dependency of changes in symptoms on MET hours and symptoms at baseline, we included these as additional predictors in the model.

RESULTS

CROSS-SECTIONAL ASSOCIATIONS

The correlations between MET hours and symptoms of anxiety and depression are given in **Table 1** together with the cross-sibling cross-trait correlations. The within-person cross-trait correlations between MET hours and anxious and depressive symptoms were small but significant, ranging from -0.06 to -0.14, demonstrating that increased exercise behavior is cross-sectionally associated with decreased anxious and depressive symptoms. The associations were somewhat stronger in women. The cross-sibling cross-trait correlations in MZ twin pairs were significant and similar in size to the within-person cross-trait correlations, indicating that exercise behavior in one twin is predictive of anxious and depressive symptoms in the genetically identical co-twin. In DZ cross-twin or sibling pairs, who share only part of their genetic makeup, exercise behavior of one sibling is not predictive of anxious and depressive symptoms in the other sibling.

Table 2. Genetic Correlation Between Metabolic Equivalent Task (MET) Hours and Symptoms of Anxiety and Depression Estimated in the Cross-sectional Bivariate Genetic Model^a

Genetic Correlation	Genetic Correlation Estimate (95% CI) Between MET Hours and				
	Depression	Anxiety	Somatic Anxiety	Neuroticism	Composite Score
In men	-0.24 (-0.36 to -0.12)	-0.16 (-0.28 to -0.04)	-0.20 (-0.35 to -0.05)	-0.16 (-0.28 to -0.07)	-0.22 (-0.34 to -0.10)
In women	-0.22 (-0.30 to -0.13)	-0.17 (-0.25 to -0.08)	-0.25 (-0.33 to -0.16)	-0.17 (-0.24 to -0.09)	-0.20 (-0.28 to -0.12)

Abbreviation: CI, confidence interval.

^aAll data are significant based on 95% CIs (computation is illustrated in Figure 1A).

Table 3. Longitudinal Within-Person Correlation Between Metabolic Equivalent Task (MET) Hours at Baseline and Symptoms of Anxiety and Depression at Follow-up Among Individuals With Data at Both Time Points

Variable	MET Hours					
	In 1991 vs Symptoms in 1993 or 1995 ^a		In 1993 vs Symptoms in 1995 or 2002 ^a		In 1991 vs Symptoms in 2002	
	No.	Pearson <i>r</i> (95% CI) ^b	No.	Pearson <i>r</i> (95% CI) ^b	No.	Pearson <i>r</i> (95% CI)
Depression	804	-0.10 (-0.11 to -0.06)	1166	-0.10 (-0.12 to -0.06)	534	-0.14 (-0.06 to 0.16)
Anxiety	1864	-0.11 (-0.11 to -0.07)	1033	-0.10 (-0.12 to -0.05)	581	-0.12 (-0.14 to -0.06) ^a
Neuroticism	1861	-0.09 (-0.10 to -0.06)	1011	-0.08 (-0.11 to -0.05)	571	-0.13 (-0.15 to -0.07) ^a
Somatic anxiety	1871	-0.07 (-0.10 to -0.06)	1017	-0.11 (-0.12 to -0.06)	571	-0.13 (-0.17 to -0.08) ^a
Composite score	725 ^c	-0.08 (-0.10 to -0.05)	991	-0.08 (-0.11 to -0.04)	520	-0.12 (-0.14 to -0.05) ^a

Abbreviation: CI, confidence interval.

^aDepression was measured in 1995; all other measures of anxious and depressive symptoms were measured in 1993 (computation is illustrated in Figure 1C).

^bSignificant based on 95% CIs.

^cComposite scores were unavailable in parents.

Bivariate Genetic Model

Estimates of the genetic correlations obtained from cross-sectional bivariate genetic models of MET hours and anxious and depressive symptoms in men and women are given in **Table 2**. Genetic correlations were significant and ranged from -0.16 to -0.24. No environmental correlations, ranging from -0.07 to 0.05, were significantly different from zero, suggesting that the association between exercise behavior and symptoms of anxiety and depression is not explained by a causal effect. Instead, common (ie, overlapping) genetic factors explain the cross-sectional association between MET hours and symptoms of anxiety and depression.

MZ Twin Intrapair Differences Model

Regression of the intrapair difference scores in anxious and depressive symptoms on the intrapair difference scores in MET hours ranged from -0.04 to 0.03 and were non-significant. Therefore, in genetically identical twin pairs, a twin who exercises more is not less depressed than his or her co-twin who exercises less, which does not support the hypothesis that exercises causes relief in anxious and depressive symptoms.

LONGITUDINAL ASSOCIATIONS

An overview of the longitudinal within-person correlations between MET hours at baseline and anxious and

depressive symptoms at follow-up is given in **Table 3**. The longitudinal correlations are significant and range from -0.07 to -0.14. Therefore, they are comparable in magnitude to the cross-sectional within-person correlations given in Table 1.

Longitudinal Correlation Between MET Hours and Symptoms of Anxiety and Depression

The genetic correlations between MET hours and symptoms of anxiety and depression, obtained from the longitudinal multivariate genetic model, are given in **Table 4**. They were significant and ranged from -0.21 to -0.40. None of the environmental correlations, ranging from -0.12 to 0.22, were significantly different from zero, suggesting that the longitudinal associations between exercise behavior and symptoms of anxiety and depression are not explained by a causal effect. Instead, common (ie, overlapping) genetic factors explain the longitudinal correlation between MET hours and symptoms of anxiety and depression.

Longitudinal Correlation of Differences Scores

Regression analyses were used to test whether a change in MET hours in an individual over time predicted a parallel change in anxious and depressive symptoms. An increase (or, vice versa, a decrease) in MET hours did not predict a decrease (or increase) in anxious and depressive symptoms during intervals of 2, 4, 7, 9, and 11 years.

Table 4. Genetic Correlation Between Metabolic Equivalent Task (MET) Hours and Symptoms of Anxiety and Depression Estimated in the Longitudinal Bivariate Genetic Model

Genetic Correlation	Genetic Correlation Estimate (95% CI) Between MET Hours and				
	Depression ^a	Anxiety ^a	Somatic Anxiety	Neuroticism ^a	Composite Score ^a
In men	-0.20 (-0.35 to -0.06)	-0.26 (-0.39 to -0.13)	-0.25 (-0.43 to 0.02)	-0.21 (-0.36 to -0.06)	-0.24 (-0.36 to -0.12)
In women	-0.34 (-0.43 to -0.24)	-0.28 (-0.38 to -0.17)	-0.40 (-0.50 to -0.30) ^a	-0.27 (-0.38 to -0.14)	-0.32 (-0.41 to -0.22)

Abbreviation: CI, confidence interval.

^aSignificant based on 95% CIs.

The estimated correlations between the change scores ranged from -0.05 to 0.05 and were nonsignificant. These results suggest that there is no evidence for a causal effect of exercise on relief of anxious and depressive symptoms in the population.

COMMENT

This study corroborates previous findings in studies^{1-10,12-15} with non-genetically informative designs that showed modest but significant cross-sectional and prospective associations of regular exercise with reduced anxious and depressive symptoms. In addition to these population-based findings, evidence from experimental studies¹⁶⁻²⁶ in healthy and clinical samples indicating decreased symptoms after standardized training programs leads to the dominant hypothesis that the association between exercise behavior and reduced symptoms of anxiety and depression derives from a causal effect of exercise. In the present study, a series of rigorous tests of this hypothesis was performed using a genetically informative design. None of these tests supported the causal hypothesis. Instead, the association of exercise with reduced anxious and depressive symptoms was explained by common genetic factors; there is a common genetic vulnerability to lack of regular exercise and risk for anxiety and depression in the population. It is unknown which genes might be involved in voluntary exercise behavior and in the risk for anxiety and depression, but genes involved in the dopaminergic, norepinephrenergic, opioidergic, or serotonergic pathways of the brain are likely candidates to simultaneously affect the regulation of exercise drive and mood.⁴⁶⁻⁴⁹

This outcome seems at odds with findings from randomized controlled trials in clinical and population samples indicating that regular exercise can relieve symptoms in subclinical individuals and in patients diagnosed as having an anxiety or depressive disorder.²²⁻²⁶ To understand the different outcomes of both types of study, it is crucial to make a distinction between the effects of prescribed and externally monitored exercise in selected subgroups and the effects of voluntary leisure-time exercise at the population level. Only voluntary leisure-time exercise is influenced by genetic factors, whereas the other type of exercise is environment driven. The absence of causal effects of voluntary exercise on symptoms of anxiety and depression does not imply that manipulation of exercise cannot be used to change such symptoms. It means that a population association, cross-

sectional or longitudinal, cannot be used to justify exercise as a treatment without an actual randomized controlled trial. The possible difference in the antidepressant effects of prescribed vs voluntary exercise is consistent with findings from a recent study²⁷ suggesting that the therapeutic effects of exercise are nonspecific to exercise. The antidepressant effects of exercise may only occur if the exercise is monitored and part of a therapeutic program.

Several limitations of this study should be noted. First, some selection bias may have been present in the sample. In general, ascertainment by twinning is a good way to obtain a random population-based sample of families, and our Dutch sample was shown to be representative of the general Dutch population in the prevalence of exercise participation and anxiety and depressive disorders, as well as with regard to socioeconomic status, smoking behavior, and religion.^{8,33,50} However, individuals from highly cooperative families (ie, families in which most individuals participate) are slightly less anxious and depressed than individuals from less cooperative families (ie, families in which only some individuals participate),³⁵ although they were not more frequent exercisers. In our study, individuals who participated in more than 1 survey were, on average, less anxious and depressed than individuals who participated only once. However, this effect was small, and the associations between exercise participation and symptoms of anxiety and depression did not decrease significantly when they were recomputed among individuals who participated more than once.

A second limitation concerns the power to detect genetic and environmental correlations in the bivariate genetic model. The correlations between exercise and anxious and depressive symptoms are small. In a bivariate genetic model with a within-person correlation of 0.10, power analyses showed that the necessary numbers of complete twin pairs are 3210 to detect the genetic correlation with a power of 80% and 3864 to detect the environmental correlation. With a within-person cross-trait correlation of 0.15, the numbers of pairs drop to 1427 for the genetic correlation and 1703 for the environmental correlation. Therefore, given the phenotypic correlations and sample sizes in this study, there was sufficient power to detect genetic and environmental correlations in women (>0.80) but only moderate power in men (>0.60).

A third limitation is that the present study could not explicitly test more complex mechanisms of causality (eg,

a combination of common genetic factors and a causal effect of exercise or reciprocal causality). These mechanisms can in principle be studied using direction of causation models developed by Heath et al⁵¹ and extended by Duffy and Martin.⁵² However, we could not apply these models to our data because they require that heritability estimates for exercise behavior and symptoms of anxiety and depression be substantially different, which they are not.²⁸⁻³⁰

A fourth limitation may be the generalizability of the results in this Dutch sample to different age groups such as adolescents and older persons and to other countries. It has been shown that the prevalence of exercise participation decreases with age.⁸ Although the relationship with anxious and depressive symptoms does not depend on age,⁸ it remains possible that causal effects of exercise are specific to certain age ranges. The prevalence of exercise participation can also differ markedly among countries, and we do not know whether the correlation between exercise behavior and symptoms of anxiety and depression, phenotypic and genetic, differs across countries and races/ethnicities as well.^{2,53}

CONCLUSIONS

To summarize, this study is the first (to our knowledge) to test the causal effect of exercise on symptoms of anxiety and depression in a population using longitudinal and genetically informative designs. The findings confirm that lower levels of regular exercise are associated with higher levels of anxious and depressive symptoms, but they falsify the causal hypothesis. These findings do not detract from the beneficial effects of regular exercise on numerous aspects of physical health such as cardiovascular disease and type 2 diabetes mellitus.^{54,55} Our results signal psychiatrists and epidemiologists that the small but robust cross-sectional and longitudinal correlations between voluntary exercise behavior and mental health should be interpreted with caution.

Submitted for Publication: October 12, 2007; final revision received March 27, 2008; accepted March 27, 2008.

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Funding: This study was supported by grants NWO-904-61-193, NWO-480-04-004, and NWO-575-25-006 from the Netherlands Organization for Scientific Research (Drs Boomsma and de Geus).

Financial Disclosure: None reported.

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